

Aspirin intolerance and asthmal induction of a tolerance and long-term monitoring

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Summary

Acetylsalicylic-acid (ASA) intolerance is well recognized as a possible cause for exacerbating asthma. It has been postulated that if this could be overcome, long-term aspirin administration could improve asthma symptoms and enable reduction of the use of other anti-asthmatic drugs.

We succeeded in inducing an ASA tolerance in nine corticosteroid-dependent asthmatics, and this tolerance lasted at least 1 month and at most 1 year. Progressive deterioration in lung function was seen, however, in all patients taking ASA for more than 1 month, unless the corticosteroid intake was increased. These results suggest that ASA long-term treatment is of no help to severe corticosteroid-dependent, ASA-sensitive asthmatics. This conclusion differs from other reports on ASA intolerance in asthma.

Introduction

Among asthmatic patients, those who present aspirin intolerance constitute a distinct sub-group. This sub-group accounts for 1·7–5·6% of the whole asthmatic population if assessed by clinical history, and for 8–22% if diagnosis is made by respiratory challenge (Szcekllick, Gryglenski & Czerniawska-Mysik, 1977; Stenius & Lemola, 1976; Weber *et al.*, 1978). For this kind of asthma, which is usually severe, associated with rhinitis and sinusitis and made worse by aspirin intake, the treatment comprises bronchodilators and corticosteroids. Aspirin (acetylsalicylic acid—ASA), and non steroidal pain relievers as well as anti-inflammatory drugs are to be avoided completely, and so are food and medications coloured with tartrazine or azo dyes, all those compounds usually inducing a severe attack, a few minutes after ingestion (Szcekllick *et al.*, 1977; Stenius & Lemola, 1976; Weber *et al.*, 1978).

After an aspirin-induced respiratory reaction there is always a temporary

refractory state (Zeiss & Lockey, 1976) that lasts 2–6 days. In this interval, further ingestion of aspirin does not cause any harm. So, to extend this refractory state it has been proposed to administer aspirin continuously to avoid unwanted reactions provoked by an accidental intake of this drug (Stevenson, Simon & Mathison, 1980; Naeife *et al.*, 1982).

In more recent studies improvement in respiratory function by long-term aspirin administration in asthma associated with aspirin intolerance has been claimed (Stevenson *et al.*, 1983; Chiu, 1983), moreover aspirin intake in some of these reported cases has allowed a significant reduction of other anti-asthmatic drug prescriptions.

It seemed important to confirm these results in severe asthmatics on continuous steroid therapy and with aspirin hypersensitivity, and to record not only subjective symptoms but also long-term pulmonary function tests.

In all patients placebo challenge was made, followed by ASA challenge which was positive. A maintenance daily treatment was undertaken the following day and followed for several weeks with monitoring of respiratory function and drug intake.

Material and methods

Patients

Nine patients (four women and five men, mean age 42 years) were studied. Informed consent was obtained in all cases.

All exhibited severe steroid-dependent asthma and in four cases sinusitis; four of them had nasal polyposis.

Clinical history was positive for aspirin hypersensitivity.

Provocation challenge and tolerance induction

All patients were stable according to physical examination and record of forced expiratory volume in 1 sec (FEV_1) at least 7 days before the challenge day (day 1)—i.e. variation in FEV_1 was less than 15% for this period. Usual treatment was kept identical during the whole procedure except for sprays of bronchodilators, ketotifen or disodium cromoglycate, discontinued 48 hr before day 1. On day 1 oral placebo was administered at three different times, 90 min apart, and FEV_1 was recorded hourly for 8 hr. On day 2 aspirin, with the same appearance and at the same intervals as placebo was administered at increasing doses: 10, 15, 50, and 75 mg, and if necessary on day 3, 100, 150, 300, and 500 mg. The challenge was positive for all patients—i.e. we observed a decrease in FEV_1 larger than 30% of the initial value in all cases. The last ASA dose was repeated on the following day, and increasing doses were then administered on this day and if necessary on 4 other days until a dose of 500 mg could be taken daily without any decrease in FEV_1 .

After this point was reached, 500 mg were administered daily.

Long-term monitoring

Each patient was then instructed to record respiratory, nasal and sinusitis symptoms, daily steroid intake and peak expiratory flow rate (PEFR) with a Wright Peak flow meter, and then dismissed from hospital. Physical examination was scheduled weekly with ASA intake during examination to avoid the possibility that patients discontinued their medication.

Statistical study

Peak expiratory flow rates (PEFR) were recorded on a daily base and a mean was established weekly and monthly. Each week or month the average PEFR was then compared to the first week or month average PEFR using a paired *t*-test.

Results

Provocation challenge and tolerance induction

For all nine patients the provocation challenge was positive with an aspirin dose ranging from 50 to 150 mg.

Symptoms were always the same. They were facial erythema, mucosal congestion with rhinorrhea or nasal obstruction, and increasing respiratory discomfort with progressive dyspnoea and wheezing. One of the patients (MY) experienced an acute urticaria but we never observed any severe systemic reaction.

Refractory state was then observed in all cases after the initial reaction was reversed with a bronchodilator. The critical dose was repeated on the following day without significant effect and could be increased without the appearance of any symptom.

All patients finally received a daily dose of 500 mg aspirin beginning on day 4, without any change in their usual medication intake.

Long-term monitoring

Four of the nine patients stopped aspirin intake, on their own initiative, because they experienced a new asthma attack after an asymptomatic interval of 15–45 days (FR, SV, M and W).

In two other patients (F and H) we stopped the aspirin administration because of the recurrence of symptoms of respiratory discomfort and nasal obstruction after aspirin intake, without evidence of respiratory or sinus infection.

Results of PEFR monitoring are reported in Table 1. All average PEFR are stable until last week as well as the steroid daily dose.

The three remaining patients (patients 1–3, Fig. 1) were still under aspirin therapy after more than 6 months.

For patient 1, steroid intake had to be increased on the second and third months, yet respiratory symptoms were still present, so steroid therapy was again increased on the fourth month with a subsequent improvement of the PEFR. Steroid daily dose was

Table 1. Summary of the unsuccessful cases for whom treatment with aspirin was stopped

Patients	Weekly mean PEFR (l/min)					PEFR before ASA (mean o/3)
	1	2	3	4	5	6
FR	412 ± 10	395 ± 17	405 ± 22	319 ± 46		405
SV	285 ± 15	280 ± 27	192 ± 38			290
M	375 ± 24	390 ± 15	355 ± 31	270 ± 42		380
W*				Urticaria		400
F	260 ± 16	255 ± 18	280 ± 27	240 ± 25	195 ± 33	290
H	334 ± 15	366 ± 24	355 ± 19	375.7 ± 17	315 ± 32	291 ± 46

* For W aspirin was stopped after 2 weeks (data of PEFR were lost).

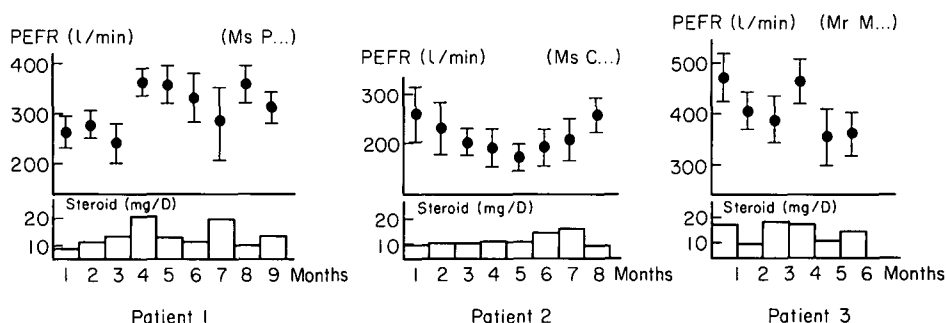


Fig. 1. Monthly changes in PEFR and steroid medication in three patients. In the upper panels the monthly average PEFR (l/min) is shown; in the lower panels the monthly average of the daily dose of corticosteroids (mg/day) is shown. Control PEFR (before ASA therapy) were respectively 260, 270 and 460 (mean of three measures).

maintained in the following month without any possibility of reduction of this dose. In this case as well, nose and throat symptoms were very well controlled under aspirin therapy.

Patient 2 (Fig. 1) showed a slow decrease in PEFR from the second month to the fifth under the same steroid therapy. Beginning on the sixth month a significant increase in PEFR appeared and was still present 8 months after the test, but steroid intake has been increased on the sixth and seventh months and that is probably the reason for this improvement. Note that a permanent rhinorrhea completely disappeared from the first day of aspirin intake.

Patient 3, in an attempt to reduce his daily intake of steroids on the second month, experienced a significant fall in PEFR and had to increase again steroid therapy at the initial level. Nasal symptoms were still present in this case.

In summary, these results show that we induced a tolerance to aspirin intake in our nine patients but in only one-third of the patients did this tolerance last more than 6 weeks. In those patients who were on aspirin for a long period of time, we always observed a progressive fall in PEFR and worsening of respiratory symptoms except if steroid intake was significantly increased. Nose and throat symptoms were reduced in two of those three cases.

Discussion

The precise pathogenesis of aspirin intolerance is not known (Szczeklick & Czerniawska-Mysik, 1976). It is not due to an allergic mechanism since intolerance is also observed with pain relievers and anti-inflammatory agents with a completely different molecular shape and composition.

A pharmacological mechanism has been proposed since all these different compounds inhibit cyclo-oxygenase that is a catalytic enzyme leading from arachidonic acid to thromboxanes and prostaglandins (Szczeklick & Czerniawski-Mysik, 1976).

In patients with aspirin-induced asthma, the possibility of inducing tolerance could be a new therapeutic approach. Moreover this tolerance could enable aspirin anti-inflammatory therapy to be used whenever needed. Stevenson *et al.* (1980) attempted to induce a long-term tolerance in 1980. They reported two asthmatic patients with aspirin intolerance in whom respiratory patterns remained unchanged,

and nose and throat symptoms improved, while on aspirin long-term maintenance. These two patients even reduced or stopped their corticosteroid medications.

Our results differ greatly: first, we lack some long-term data since four patients spontaneously stopped the aspirin therapy because of occurrence of asthma. It is difficult to ascertain whether or not these attacks are really aspirin-related since the patients were used to exacerbations due to infection or other events, even while under continuous heavy medication.

In the two other patients we had to stop the aspirin intake because they showed the same symptoms as those observed during the challenge, in these two cases aspirin is presumably the cause of a rapidly progressive deterioration of respiratory function.

In the three remaining patients, followed for more than 6 months, respiratory function tests showed a progressive worsening, without any possibility for decreased steroid daily intake. In such an open study it is difficult to be sure that aspirin was the only cause of this evolution, since we do not have any placebo group for comparison. But the absence of a control group should not be so important for interpretation of results since we report negative results in the patient group, and this negative result is the important finding. No respiratory improvement was seen in any patient in short- or long-term monitoring, in our aspirin-treated patients.

Naeife *et al.* (1982) in a similar survey found different results in that sixteen patients were treated with 650 mg aspirin daily for 2–24 months. In ten of the sixteen there was an improvement in respiratory function, but evidence was not presented that they were very severe, corticosteroid-dependent asthmatics, as were our patients. Stevenson *et al.* (1983) found in their twenty-five patients studied in a random double-blind study an improvement in seventeen cases, with respiratory subjective improvement in eleven cases, independent of the dose of aspirin, but none of the patients could reduce his corticosteroid intake, presumably because their condition remained severe. Therefore, in our experience, aspirin tolerance did not confer any respiratory long-term benefit, in disagreement with previous reports. However, aspirin long-term administration improved nose and throat symptoms in our patients as it did in other studies (Lumzy *et al.*, 1983). This aspirin tolerance induction is very interesting for patients who need such treatment or other related anti-inflammatory therapy, but it does not improve respiratory function on a long-term basis.

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